Benzothiazole- and Morpholine-Based Thiazoles Category Justification and Testing Rationale

CAS Nos.: **95-32-9 and 103-34-4**
(+CAS Nos. 95-16-9, 102-77-2, 110-91-8, 149-30-4 and 120-78-5 for data purposes)

Rubber and Plastic Additives Panel
American Chemistry Council
December 2003

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council includes the following member companies: Alco Chemicals; Bayer Polymers LLC.; Ciba Specialty Chemicals Corporation; Crompton Corporation; Eliokem, Inc.; Flexsys America L.P.; The Goodyear Tire & Rubber Company; The Lubrizol Corporation; Noveon, Inc.; and, R.T. Vanderbilt Company, Inc.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives (RAPA) Panel hereby submits for review and public comment their revised test plan for the Benzothiazole- and Morpholine-based Thiazoles (BMBT) category of chemicals under the High Production Volume (HPV) Chemical Challenge Program. Based on EPA's comments (dated September 6, 2002) on the Benzothiozole-based Thiazole category as originally conceived, RAPA has created two separate categories from the original Benzothiazole-based Thiazoles category. The new categories are the BMBT category, which is the subject of this submission and the Benzothiazole-based Thiazole category, which is the subject of a separate submission (dated July 17, 2003) and which no longer includes chemicals containing morpholine. While some characteristics of many of these chemicals overlap, RAPA has made this category revision to more clearly explain and substantiate the category justifications. RAPA also is providing supporting information for benzothiozole and additional supporting information for three new surrogate chemicals. Furthermore, RAPA is providing a tabular summary of data on morpholine (CAS No. 110-91-8) that is available in the current IUCLID Data Set and is referencing information provided to EPA in the ACC Amines Panel's test plan and robust summary for morpholine under the International Council of Chemical Associations (ICCA) HPV program. The robust summary for morpholine has already been submitted to EPA by the Amines Panel and, therefore, is publicly available for review. In addition, 4,4'-dithiodimorpholine (CAS No. 103-34-4), a chemical volunteered for data submission in 2003, is now included in the BMBT category.

As discussed in the report that follows, chemicals in the BMBT category, which are used primarily as cure-rate accelerators or sulfur donators in natural and synthetic rubbers or as chemical intermediates in

benzothiazole group [benzene ring + thiazole ring] or another morpholine group via a sulfur or sulfur-sulfur bond. Their use in the rubber vulcanization process requires stability at high temperatures, low biodegradation, negligible water solubility and low vapor pressure. Non-rubber applications for this category include metal chelation, ore flotation, corrosion inhibition, veterinary drugs and industrial biocide/water treatment for 2-mercapto-benzothiazole and sodium 2-mercaptobenzothiazole.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted an extensive literature search for all available data, published and unpublished. The Panel has also performed an analysis of the adequacy of the existing data and developed a scientifically supportable category of related chemicals and used structure-activity relationship information to address HPV requirements.

Existing data for members of this category indicate that they are of moderate concern for aquatic toxicity, low concern as Persistent Organic Pollutants (POPs), moderate concern for skin irritation/allergic skin reaction, and low concern for mammalian toxicity and carcinogenicity. In addition, the Food and Drug Administration has approved several food-contact uses for this category of chemicals. The RAPA Panel concludes that there is sufficient data on the members of this category and no additional testing is recommended for purposes of the HPV Program.

Benzothiazole- and Morpholine-Based Thiazoles Category

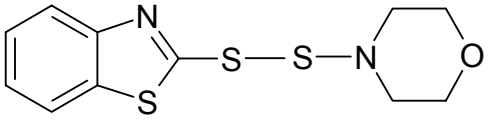
According to guidelines for the HPV Chemical Program, a chemical category is "a group of chemicals whose physico-chemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

Relying on several factors specified in "Development of Chemical Categories in the HPV Challenge Program,"[1] in which use of chemical categories is encouraged, the following closely related chemicals described in Figure 1 constitute a chemical category.

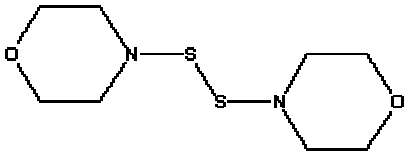
Structural Similarity

A key factor supporting the classification of these chemicals as a category is their structural similarity (See Figure 1). All materials in this category contain a morpholine group attached to a benzothiazole group [benzene ring + thiazole ring] or to another morpholine group via a sulfur or sulfur-sulfur bond.

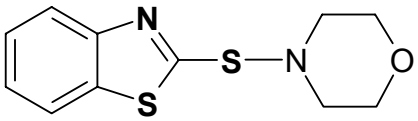
[1] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm.



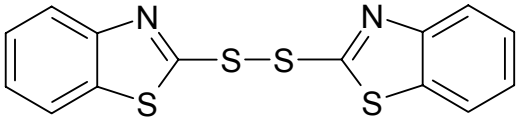
95-32-9
Benzothiazole, 2-(4-morpholinyldithio)-
(Morfax)



103-34-4
4,4'-Dithiodimorpholine
(DTDM)

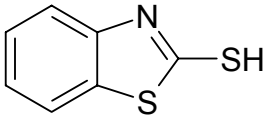


102-77-2
N-oxydiethylenebenzothiazole-2-sulfenamide
(MBS)

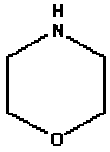


120-78-5

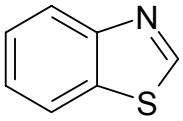
(MBTS)



149-30-4
2-Mercaptobenzothiazole
(MBT)



110-91-8
Morpholine



95-16-9
Benzothiazole
(BTH)

Figure 1. Chemical Structures for Members of the BMBT Category

Morfax and DTDM are the HPV chemicals of interest in this category. N-oxydiethylene benzothiazole 2- sulfenamide (OBTS) and 4,4'-dithiodimorpholine (DTDM) are structurally similar to Morfax. OBTS is composed of the same basic components, mercaptobenzothiazole and morpholine joined by a sulfur atom, while DTDM contains the sulfur-sulfur-morpholine configuration found in Morfax. The similar molecular weights also indicate that OBTS and DTDM are good surrogates for Morfax (see Table 1). However, because Morfax has been shown to hydrolyze to MBTS and morpholine (Luecken and Sullivan, 1981; Lawrence, 1976), data on morpholine that were obtained from the ACC Amines Panel's robust summaries and test plan also are referenced as surrogate data in support of Morfax. MBTS has been shown to be metabolized to MBT as reported to EPA under TSCA Section 4 testing for MBT. EPA also considered Morfax for TSCA Section 4 testing and determined that further testing was not needed. The Panel believes that these data fully brackets the chemistry of Morfax and DTDM and provide adequate data to predict the physical properties, environmental fate, and hazards of this chemical.

Common Precursors

All category members are formed by the reaction of morpholine with benzothiazole or another molecule of morpholine in the presence of a sulfur donator.

Common Breakdown Products

2-Mercaptobenzothiazole and/or morpholine are the ultimate chemicals formed when these compounds undergo hydrolysis and/or metabolism.

Similarity of Physical Chemical Properties

The physical chemical properties of Morfax, DTDM and the other structural analogs parallel their structural similarity. All have molecular weights that are close to each other and exhibit limited water solubilities, low vapor pressures, high flash points, high boiling/decomposition points, excellent thermal stability, lack of reactivity, and Log P values at or below 5. Not unexpectedly, a few of the physical chemical properties for the hydrolysis products/metabolites are different than the parent compounds. For purposes of the HPV program, the existing data are adequate to describe the physical chemical properties of the category and/or for extrapolation (read-across) to members.

Fate and Transport Characteristics

The members of this category (parent compounds) are expected to distribute primarily in soil and water (Table 2) and have been shown to rapidly hydrolyze to their starting materials, especially under acidic conditions. These parent compounds are not readily biodegradable when measured by CO_2 evolution, mineralization or hydrolysis, and marginal by indirect photolysis. Testing and published literature has shown that, if hydrolysis occurs, the primary hydrolysis product will be MBTS, ultimately MBT, and morpholine. Morpholine is readily biodegradable, while MBT is not. Photodegradation is expected to have minimal impact on overall degradation. For purposes of the HPV program, the existing data is adequate to describe the environmental fate and transport of the category and/or for extrapolation (read-across) to members.

Table 1. Physico-chemical Properties of Benzothiazole- and Morpholine-based Thiazoles Category

Chemical CAS No.	Benzothiazole 2-(4-morpholinyldithio)- 95-32-9	4,4'-Dithiodimorpholine 103-34-4	N-Oxydiethylene Benzothiazole 2-sulfenamide 102-77-2	Benzothiazole Disulfide (SIDS) 120-78-5	Morpholine (ICCA) 110-91-8	2-Mercapto benzothiazole 149-30-4	Benzothiazole (SIDS) 95-16-9
Molecular Weight	284.42	236	252.4	332.38	87.12	167.24	135.18
Melting Point	128.6˚C	130˚C	75-90˚C 150.7ºC (EPI)	180˚C	-5° C	181˚C	2˚C
Boiling Point	Decomp. 207.5˚C	334.98°C	Decomp. 385˚ C (EPI)	Decomp.	128-130° C	Decomp. above 260˚C	231˚C
Relative Density	1.51g/cm3	1.36g/cm3 @25˚C	1.35g/cm3 @20˚C	1.54g/cm3 @25˚C	1 g/cm^3 @ 20° C	1.42g/cm3 @20˚C	1.246g/cm3 @20˚C
Vapour Pressure	1.16 x10(-7) hPa @25˚C (EPI)	3.55 x10(-5) hPa @25˚C (EPI)	1.34 x10(-6) hPa @25˚C	5.97 x10(-10) hPa @20˚C	10 hPa @20° C	3.0 x10(-6) hPa @25˚C	0.018 hPa @20˚C
Partition Coefficient	1.59 (EPI)	2.49 @ 25°C	3.49 1.025 (EPI)	4.5 (4.66 EPI)	-2.55 @ 25° C	2.4 (2.86 EPI)	1.94 (2.01 EPI)
Water Solubility	657.6 mg/l @25˚C (EPI)	237 ppm @25°C	32ppm 3 gm/l @ 25˚C (EPI)	80 – 96 mg/l @22˚C pH 5.0	5 g/l @ 25° C pH 10.6 miscible	118mg/l @25˚C pH 7.0	3.5g/l @20˚C

= Non-sponsored chemicals used for data purposes only

EPI = EPIWin Modeling Program. Meylan W. and Howard P. (1999) Syracuse Research Corporation.

Table 2. Environmental Fate of the Benzothiazole- and Morpholine-based Thiazoles Category

Chemical **CAS No.**	**Benzothiazole 2-(4-morpholinyldithio)-** **95-32-9**	**4,4'-Dithiodimorpholine** **103-34-4**	**N-Oxydiethylene Benzothiazole 2-sulfenamide** **102-77-2**	**Benzothiazole Disulfide (SIDS)** **120-78-5**	**Morpholine (ICCA)** **110-91-8**	**2-Mercapto benzothiazole** **149-30-4**	**Benzothiazole (SIDS)** **95-16-9 (SIDS)**
Hydrolysis	Hydrolyzes	$T_{1/2}$ = 168 hr @ 23°C pH 7.0	$T_{1/2}$ = 1.1 hr (AOP) $T_{1/2}$ = 1 hr (water)	37% (7 days)	Addressed by Amines Panel ICCA	0-15 % (7 days)	No adequate data were located
Biodegradation	No adequate data were located	76% (49 days, 20.1 mg/l)	0% (28 days)	0-2 % (28 days)	91% (21 days) Readily Biodegradable	< 1 % (28 days)	0% (28 days,100 mg/l) >65% (21 days, 0.8mg/l)
Photodegradation (T ½)	0.37 hr (air; EPI)	0.34 hr (air; EPI)	1.1 hr (air; EPI) 1 hr (water; EPI)	0.4 hr (air; EPI) 3 hr (water)	< 1 day	2.4-4.8 hr (air) 31 min (water)	0.76 hr (air; EPI) 110 days (water)
Fugacity Level III (distribution)	(EPI)	(EPI)	(EPI)	(Calculated)		(EPI)	(EPI)
Air	< 0.1 %	0.00389%	<0.01%	< 0.1 %	0.0955%	0.507 %	23.3 %
Water	36.6 %	24.8%	44.6%	17.2 %	56.1%	35.9 %	56.4 %
Soil	63.3 %	75%	55.3%	72.7 %	43.8%	63.4 %	20.1 %
Sediment	0.09 %	0.175%	0.0904%	10.2%	0.0934%	0.172 %	0.16 %